Part 3: Good Manufacturing Practice

CHAPTER 26

Introduction: Good Manufacturing Practice

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"Simply put, GMP is the means by which the patient gets the medicine that he or she expects – and nothing else." — Anon.

26.1 INTRODUCTION

It is generally accepted within the pharmaceutical industry that a system of control is essential to ensure that medicinal products are manufactured to required standards. The term good manufacturing practice (GMP) is universally used to describe the system or systems upon which this assurance is based.

GMP is applied, regulated and controlled in different ways across the Globe. Within the United States of America GMP is described in the Code of Federal Regulations (CFR) in a surprisingly short series of paragraphs commonly referred to as "the CFRs."[1] The USA also adds the word "current" and thus abbreviates the term to cGMP. Although the CFRs are apparently written as rigid mandatory regulations, the US regulatory agency, the Food and Drug Administration (FDA) expects industry to constantly improve standards through advanced technology by using the FDA's guidance documents or by following case law. A particularly useful way to sense the FDA's current thinking on standards within the industry and how they should change is by reading the "warning letters" issued to companies whose operations fall short of expectations, which are published in a redacted form on its website.

At the time of writing the FDA has issued a major report detailing a revised approach to the application of GMP in the 21st century, which it considers should be based on a sound quality system but also encompass comprehensive risk assessment at each point of the process.[2]

Within the European Union (EU), GMP is imposed by two Directives which state that manufacturers of human and veterinary medicinal products must carry it out.[3,4] Two further Directives lay down the principles and guidelines of GMP[5,6] while a fifth imposes GMP on the manufacturer of an investigational medicinal product (IMP).[7]

The principles of GMP expressed in Directives 2003/94/EC and 91/412/EEC are brief legal statements of what GMP actually is which should be read and followed with care by the manufacturer (As 91/356/EEC the human GMP Directive was almost identical to the veterinary version, simply being a legal nicety to separate human and veterinary legislation. The recent requirements for GMP of IMPs forced additions to the Articles and repeal of the original

Directive). Nevertheless, those responsible for the regulation of medicinal products within the EU recognised that the industry needed more detail to help interpretation. The Directives make provision for detailed guidelines to be published to which manufacturers and "agents of competent authorities" (regulatory bodies of Member States) should refer.[8] (These detailed guidelines will hereinafter be referred to as the "Guide to GMP".)

Other countries or trading blocks have similar provisions for their own interpretations of GMP. Since the USA and Europe host a massive concentration of the pharmaceutical industry (and buy a lot of its products) this chapter will describe the interpretations of GMP with respect to those two systems but it is reasonable to assume there are no major conflicts of interpretation with other systems.

26.1.1 Why is Good Manufacturing Practice Required?

Medicines are required to meet the criteria of safety, efficacy and quality before they are granted an authorisation for manufacture and sale. The first criterion is examined during the application process when a balance must be struck between safety and the product's clinical use. Simply put, will the product harm the patient more than the illness itself? Efficacy is shown by extensive clinical trials (Part 1). Will the product actually treat or alleviate the condition for which it is intended? Quality is determined by the total of the product formulation and design, its ingredients and packaging, the way the product is put together, the environment while it was manufactured and manner of storage during its lifetime. If the formulators' vision for the product is to be maintained consistently from batch to batch and dose-to-dose, the manufacturer must have suitable controls to maintain quality.

If the complex set of operations necessary to manufacture and pack medicinal products is considered, the need for control becomes obvious. Raw materials are purchased, tested, stored, dispensed (measured or weighed) and put together by some means to provide a product which must be tested then packaged using components which have usually been obtained from another party. Added to this are the complications of monitoring the environment to which the product is exposed, taking suitable samples and checking the series of records for each batch of product. Manufacturing and testing equipment must be qualified, maintained and calibrated. All those involved in the process must be suitably qualified and trained according to the job they have to do and the responsibilities they hold.

Even in the smallest of facilities where simple products are manufactured there is the opportunity for operations to fail, due to human error, equipment breakdown or just occasionally sheer bad luck. When this happens, the systems in place must ensure the product will not reach the patient without a full evaluation to confirm it meets its quality requirements.

An attractive but unsafe way to determine quality is to take samples and carry out laboratory testing. If the sample fails to meet the required specification then it might show that something has occurred during the manufacturing process. If the sample meets the specification then it is only an indication but not an absolute certainty that the remainder of the batch is satisfactory. To be sure every dose is satisfactory means testing every dose. Obviously that is not possible because to test every single dose using conventional analytical methods would destroy the whole batch. Regulators and industry alike have long recognised that relying on sample results is fallacious. Thus, assurance of quality through GMP is the accepted alternative.

26.1.2 What is Good Manufacturing Practice?

The definition of GMP found in the European Directives[5,6] is:

> *"... the part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use."*

Table 1 *Section and chapter headings of the CFRs and the Guide to GMP*

USA code of Federal Regulations Part 211	*Guide to good manufacturing practice*
	Quality management
Organisation and personnel	Personnel
Buildings and facilities	Premises and equipment
Equipment	
	Documentation
Control of components and drug product containers and closures	
Production and process controls	Production
Packaging and labelling control	
Holding and distribution	
Laboratory controls	Quality control
	Contract manufacture and analysis
	Complaints and product recall
	Self-inspection
Returned and salvaged drug products	

The same Directives define pharmaceutical quality assurance as:

> *"... the sum total of the organised arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use."*

While there is no definition given in the USA CFRs it seems to be an assumption that GMP (or more correctly, cGMP) is the total application of the regulations laid down, for in the absence of conformance with any one of them, the product is considered to be "adulterated".[9]

Official definitions are all very well for legal purposes but they give no clear indication of what is actually involved in the implementation or application of GMP. On that score there is no shortage of information for the manufacturer. The regulations and guidance documents lay down only the primary expectations.

Table 1 provides a comparison between the contents of the CFRs and the Guide to GMP. It is clear that the USA approach is more specific in detail than the European document although each regulatory authority effectively covers all areas in some way, for example the specific requirements for tamper-evident packaging found in the CFRs are imposed by other regulations within Europe.

Additional guidance for specific products, or for areas of interest demanding detailed guidance from the regulators, is provided in a series of Annexes to the Guide to GMP. The FDA also publishes "Guidance for Industry" documents, which spell out detailed requirements on specific manufacturing situations. Information on how a regulator might treat a particular aspect is given in the FDA's specific "Inspection Guides" intended as aids to its investigators. Inspectors in the rest of the world turn to the PIC/S guidance and recommendation documents for inspectors.[10]

Thus, there is no shortage of regulations, official guidance and advice on GMP although the sheer volume seems overwhelming to the industry initiate. For clarification it is useful to refer to the Guide to GMP and examine each of its chapters in turn, illustrated by examples both of good practice and what happens when it is not followed.

26.2 ELEMENTS OF GOOD MANUFACTURING PRACTICE

The nine chapters in the Guide to GMP cover all the elements involved within the pharmaceutical manufacturing operation. Some clearly overlap or cover identical requirements to the CFRs. Others contain some aspects of the CFR expectations without the precision of the US regulations. The imprecision of the Guide frustrates some but is not surprising. It is intended to cover the full

spectrum of the industry, from complex and lengthy biotechnical operations, to simple, rapid batch manufacturing. It must also be interpreted within each of the Member States of the EU, which by no means resembles the federal nature of the USA. In this way each manufacturer can ensure compliance while being able to manage operations in a flexible way.

26.2.1 Quality Management

Within the first principle of the first chapter on GMP is the requirement for the holder of a manufacturing authorisation to have a "comprehensively designed and correctly implemented system of Quality Assurance (QA) incorporating GMP and thus quality control (QC). It should be fully documented and its effectiveness monitored." The QA system is expected to cover aspects even from the design through to distribution and, if it becomes necessary, recall of the product. A quality system must set out the roles and responsibilities of those persons involved.

How does one define a QA system? In setting up a manufacturing site the first step should be to map out the process. The basic elements of such a map are shown in Figure 1, but it omits areas of detail. It is not hard to envisage the many additional processes that must be added to each basic block. For example, appropriate qualified personnel must be recruited and trained for each job, equipment purchased, installed and qualified and maintained and calibrated properly. Processes require scale-up from development to full size and must be validated.

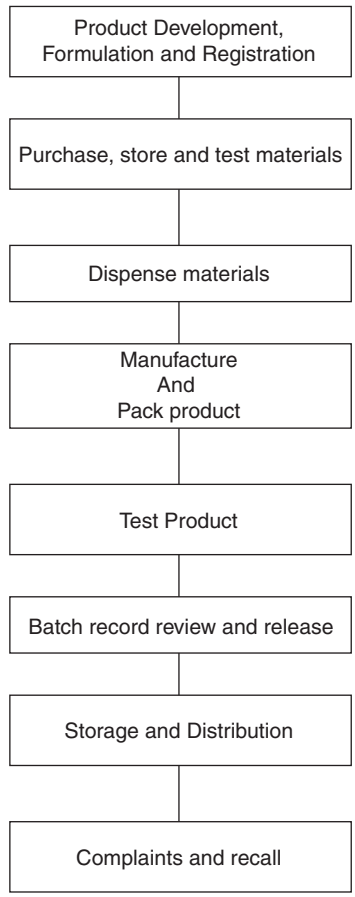

Figure 1 *Basic steps in the pharmaceutical manufacturing process*

Quality management systems are discussed elsewhere in this book (Chapter 40). However, the general design of such systems tends to be common. A set of top-level statements of policy sets out management intent on key areas of the manufacturing process. A second level series of guidance documents expands on how the intent is to be turned into practice. Third and fourth tier documents set out operation procedures in detail and provide records of operations and results.

The objective of the QA system is to ensure that decisions are not made on an ad hoc day-to-day basis, depending on circumstances or urgency. Decisions should, in effect be made by the system itself. Management's role is to monitor that the system operates satisfactorily and will maintain control of the pharmaceutical manufacturing operations.

A useful example is the way that Change Control should be managed. The manufacturer has an obligation to make the medicinal product according to its marketing authorisation and must not deviate from it unless a variation is submitted to the appropriate authority and approval has been received (various authorities differ in the extent and manner of submissions of variations before approval is given but the principle remains the same). Without procedures underwritten by clear policy from management, changes, which are not reviewed by appropriate people and which are not authorised, can rapidly shift compliance to non-compliance.

Example 1: It is tempting for the purchasing department to buy-in a raw material from a less expensive source and to persuade the laboratory to test and approve it. Production may find that material from the new source requires a change to the manufacturing process to achieve the product specification. In achieving one specification it might lose control over another–hardness of a tablet at the expense of thickness is a good example. The thicker tablet does not fit its blister pack quite so well, leading to a stability problem and a shorter shelf life.

Example 2: The site laboratory suffers a breakdown of an analytical instrument. It conveniently finds a laboratory within another company close by with a similar instrument and arranges for the samples to be tested there. This second laboratory is not listed on the company's manufacturing authorisation as an alternative testing site.

The company policy on adherence to the marketing and manufacturing authorisations should be clear. If a change-control system had been in place which required review and approval by all interested parties, backed up by submission to the regulatory authority, then the loss of control shown by these examples would not happen.

26.2.2 Personnel

If there is one area of adherence to GMP that can make or break a pharmaceutical company it is in relation to the people it recruits, trains and develops. The Guide to GMP requires "an adequate number of personnel with the necessary qualifications and practical experience." It is up to the manufacturer to decide what each of these adjectives mean in relation to the operations in question but it is not hard to envisage that each one can lead to animated discussion!

Particular requirements are quite clear. There must be an organisation chart and there must be two key personnel, the Head of Quality Control (QC) and the Head of Production, who must be independent from each other. Under European law there must also be a third individual known as the Qualified Person (QP), unless one of the first two can also act in this capacity.

It is worth noting here that the CFRs do not demand named individuals but do require a "QC unit". In many recent (1998–2003) warning letters the FDA has cited the absence of a quality unit as the main reason why a company has failed to meet GMP requirements. It must be assumed that if there is a "QC unit" there must be someone at the head of it, whatever their title.

The Heads of Production and QC have individual and shared responsibilities which can be summarised as follows:

The Head of the Production Department should:

- ensure products are produced and stored correctly
- approve instructions relating to production and ensure strict implementation
- ensure production records are evaluated and signed
- check maintenance
- ensure validations are done
- ensure training is carried out.

The Head of the QC Department should:

- approve or reject materials and products
- evaluate batch records
- ensure testing is carried out
- approve specifications and other QC procedures
- approve and monitor contract analysts
- check maintenance of his department
- ensure validations are done
- ensure training is carried out.

Shared responsibilities include:

- authorisation of procedures
- monitoring and control of the environment
- hygiene
- process validation
- training
- approval and monitoring of suppliers
- approval and monitoring of contract manufacturers
- designation and monitoring of storage conditions
- retention of records
- monitoring compliance to GMP
- inspection, investigation and taking of samples to monitor factors which may affect product quality.

It is well worth noting that training figures both as an individual and shared responsibility for the named Heads, emphasising the importance of this topic. Untrained personnel operating within the manufacturing, packaging and testing environment are dangerous, since they can act in an unaware, albeit well-meaning way.

Example 3: An untrained packaging operator picked up an apparently good pack of product from the floor and put it back on the nearest packaging line, where it was assembled with others. The pack actually came from an adjacent line packing product with the same name but of a higher strength. Because the high strength pack was collated amongst others of low strength it went unnoticed in the dispensary and a patient suffered serious side effects.

Example 4: An untrained dispensary operator did not appreciate the difference between two materials which were identical except for a different suffix on the label which indicated the viscosity grade. The material was used in a tablet granulation which seriously affected dissolution of the product in vivo.

These are typical examples of actions carried out by individuals who were unaware of the serious consequences of simple mix-ups. Proper and thorough training, repeated and updated on a regular basis, is essential within the pharmaceutical-production environment. Such training must include all those who work directly on production, packaging or testing but attention should also be given to those whose activities take them into the production or testing areas on an occasional basis, for example maintenance engineers. Office-based personnel who work in purchasing, human resources and finance should be taught which areas they can access without an escort, if any, what to wear and how to behave when in them.

Key personnel and those in responsible positions should have appropriate qualifications to understand the theoretical basis of the activities they carry out. An important example is the facility that manufactures sterile products. It should be managed and supervised by graduates with a microbiology or biology qualification who appreciate the very special requirements demanded. Some authorities require any aspect of pharmaceutical production to be supervised by a pharmacist.

26.2.3 Premises and Equipment

26.2.3.1 Premises. As a general rule, production facilities must be located in an area which will not adversely affect the operations carried out within. The design and construction must also suit the activities. However, often the managers of a pharmaceutical factory are faced with a "*fait accompli*" when it comes to the facilities in which they operate. The operation may have started many years before when the facility was newly built but since then the products handled within and the activities of any factories surrounding the site may have changed dramatically. Nevertheless the managers have a responsibility to develop the facilities, upgrade and adapt them as required, to accommodate the changing circumstances. If the external environment becomes contrary to the operations, for example in the worst case, next to a land-fill site for waste and rubbish which attracts vermin and flies, there may be little choice but to move. It may be possible in less serious situations to ensure that the external activities will not affect the products. In any case there is an obligation to keep out insects and other animals and to monitor the effectiveness of any programme to do that.

It is an expectation of GMP to maintain premises and to keep them clean and hygienic. It therefore follows that they should be appropriately lit with temperature and humidity controls to maintain suitable working conditions which permit these requirements.

Operations which might cause serious contamination of medicinal products with toxic materials, are not permitted. Thus production and storage of non-medicinal products and especially pesticides and herbicides are not allowed in the same facility although certain cosmetics may be (Note, however, that in the case of veterinary ectoparasiticides it is permitted to manufacture in pesticide specific areas in the same premises as other veterinary products).[11] It is expected that highly sensitising materials such as penicillins are produced and handled in separate facilities altogether. Other products, including certain other antibiotics, hormones, cytotoxics, and other highly active drugs should have dedicated areas although production on a campaign basis can be authorised. If so, validation of the cleaning and changeover procedures must be thorough.

An aspect which cannot be over-emphasised for any facilities but especially in storage, production and laboratory areas, is the provision of sufficient space. Lack of space causes many examples of cross contamination, mix-ups and deterioration of product or packaging.

Example 5: During a period of intense production activity in one facility, storage space within the warehouse came under pressure. As a consequence the general rule of "one item – one pallet" was ignored and boxes of leaflets for two different products were stored next to each other on the same pallet. The wrong boxes were included in a consignment to the packaging line and the

leaflets packed in the product. Luckily the mistake was spotted in a pharmacy but the subsequent recall was very embarrassing for the company.

The materials of construction and finish for any area must be appropriate to the activities carried on within. Surfaces must be smooth to allow cleaning operations to be effective but must also be of suitable materials so as not to shed particles or contaminate the product. Floor surfaces in particular must be sound and capable of withstanding vigorous cleaning agents. There are many proprietary materials for all surfaces and the manufacturer is well advised to search extensively for suitable items and to seek advice from other manufacturing sites as to their experience with various options.

Personnel should be provided with separate facilities for rest and refreshment. The wearing of working clothes in refreshment areas should be avoided if at all possible and certainly should be forbidden where facilities are shared with non-production personnel and visitors. Suitable areas should be provided for personnel for changing clothes and for washing and toilets.

26.2.3.2 Equipment. The Guide to GMP is surprisingly short in its treatment of equipment. This is remarkable when considering the effect of improper, poorly maintained and uncalibrated equipment on the quality of the final product. The range of processes covered by pharmaceutical equipment is enormous, from simple measurements through complex processing operations to huge packaging lines. Additionally, equipment is often serviced not by the production department that uses it but by an engineering department reporting separately to senior management. A particular aspect required of the Quality System is that such relationships are well organised and properly managed. Repair and maintenance activities result in engineering operatives moving from area to area with the potential for cross-contamination from their work clothes.

The first requirement of a piece of equipment is that it will not harm the product exposed to it and should do the job it is intended for. Thus it should be constructed of suitable materials. Those parts coming into contact with the product should not react with it nor release or absorb any materials. If plastics are used this may be of special importance.

Nowadays, it is a generally expected requirement of GMP that all pieces of equipment that affect quality will be subject to a systematic maintenance programme. Aspects of such a programme which ensure it will be effective are:

- a master list of equipment
- designation of quality critical and non-critical equipment
- a schedule of maintenance for each piece which specifies among other things which parts may be changed without seeking further authority
- procedures to specify action if the maintenance interval is delayed or missed altogether
- records of maintenance showing any parts that were changed or adjustments made
- procedures to remove any piece of equipment which becomes defective, redundant or obsolete.

Example 6: A maintenance engineer was called to replace an 'O' ring in the seal of a valve. The material was supposed to be black neoprene, deliberately chosen so that any particulates it released would be immediately visible. The engineer did not have a similar replacement and inserted a white nylon ring instead. White particulates were later found in an injectable product produced with the equipment.

It is expected that measuring equipment will be subject to a planned calibration programme with similar aspects to the above.

Additionally there must be strict procedures to be followed in the event that:

- a calibration interval is delayed or missed
- the instrument is found to be outside its calibrated parameters.

In the last case any action should include a review of all those batches of product which might have been affected by an incorrect measurement.

Each piece of equipment should have a log book(s) or similar record(s) which records all maintenance, calibration and cleaning carried.

26.2.4 Documentation

The quality of a company's documentation system reveals the quality of its Quality Assurance System. Documents should be clearly written, well laid out, easy to follow and with sufficient room to fill in information and results where needed. Those who manage the documentation system must ensure that documents are maintained up-to-date and that only current documents are made available to the operations. It is especially important that necessary changes to documents can be carried out within a short time. Needless bureaucracy that hinders and delays corrections to typographical errors or obvious mistakes leads to frustrations and continued use of the incorrect document, probably with hand-written amendments. This effect, which is frequently found when document management is poorly controlled or left to junior staff, is a significant indicator of a weak QA system, not as some would have it, the opposite.

The Guide to GMP sets out the minimum requirements for various documents expected to be found in the manufacturing site. The four basic types of document are stated to be Specifications, Manufacturing Formula, processing and packaging instructions, Procedures (Chapter 27) and Records. The latter is further subdivided into records of Receipt, Sampling, Testing and Other procedures including for example Validation, Pest Control and Recalls. Figure 1 suggests that there must be many other examples within the system. It is also a reminder that a document system should be designed as part of the QA system. Proper design leads to minimisation of the number and type of documents used. An example of poor design is the proliferation of similar procedures covering minor differences.

> *Example 7: A company had separate procedures to cover each type of change within its operations e.g. materials, processes, packaging and test methods. The evaluation of each change and the form used to control them was actually almost identical. This system also failed to recognise that many related minor changes actually made one critical change. By consolidating the separate procedures the company eliminated many pages of repetitive procedures and related changes were properly evaluated for their overall effect on the quality of the product.*

Thus a valuable action by auditors is to ask for a list of standard operation procedures, choose those which seem similar to each other and on examination, compare them for similarities or as more often happens, conflicts between identical activities in different areas.

26.2.5 Production

26.2.5.1 General. It is axiomatic that production operations must be performed and supervised by competent, suitably qualified and trained people. It is also a basic, maybe obvious but not always followed expectation that all operations will be carried out in accordance with written procedures (Chapter 27).

26.2.5.2 Prevention of Cross-Contamination in Production. Manufacturers should be aware of the risks of contamination of starting materials or products by another material or product, potentially with harmful effect to the patient. Particular hazards are present in facilities handling highly sensitising materials, biologicals, living organisms, hormones, cytotoxics and other highly active materials. Injectable products, those administered in large doses or over a long period of time, present a particular risk if contaminated.

Thus the manufacturer should make efforts to avoid cross-contamination. It may be possible to do this effectively in a number of ways, depending on the circumstances and the products involved. Total segregation of facilities is an obvious but expensive option, which may be unavoidable in certain instances. Lesser options include the provision of air-locks between areas at risk or providing independent air-handling units. Organisational arrangements such as ensuring that one person does not work on different products without a change of clothing may be effective. In any case, cleaning, decontamination and monitoring procedures should have demonstrated effectiveness. Test methods used for residues should be evaluated for their ability to detect the very low levels that may be present.

26.2.5.3 Validation. Significant additional guidance on validation was introduced by the relatively recent inclusion of Annex 15 in the Guide to GMP. Nevertheless some general principles are worth repeating here:

- all manufacturing processes should be validated
- significant amendments to processes should undergo evaluation to check whether re-validation is necessary
- all processes and procedures should undergo periodic re-validation to ensure they remain capable of achieving the intended results.

Validation activities should be carefully recorded as this record is useful in examining the cause of problems and deviations that occur when the process is used repeatedly.

26.2.5.4 Starting Materials. Since starting materials are fundamental to the quality of the final product the manufacturer should ensure that procedures for selection and control of suppliers are sound. An "approved suppliers list" should be maintained by the quality unit. This should be accessible to all those who handle materials or who deal with supplies such as warehouse personnel, sampling and testing staff and purchasing. Additions or deletions to the list should be controlled by the company change control procedure. Materials received from unauthorised suppliers should be returned or quarantined pending formal approval.

Materials receiving procedures should ensure that each container is checked for proper labelled identity and is of the material ordered. If several batches of the same material are received together they must be separated and controlled by internal company batch numbers. Each container should be formally sampled and tested to ensure the identity of the contents, unless an evaluation of the suppliers quality system has shown this to be unnecessary.

It is expected that materials will be properly stored, free from the possibility of mix-up and contamination and in a suitable storage area which is temperature and if needed, humidity controlled. A system of re-evaluation should be in place with an assigned retest or expiry date to each batch of material.

Only materials which have been released by QC should be used. They should be dispensed in designated areas by properly trained operators (see example 4 above), and an independent check of the identity and weight or volume must be made. They must be labelled properly.

> *Controversy exists with respect to the definition of "an independent check." Whilst a first interpretation might be that a second person is required most European authorities would probably accept a separate check by bar code reading equipment backed up by a printout from the weighing equipment. The CFRs clearly require a second person.*[12]

26.2.5.5 Processing Operations: Intermediate and Bulk Products (Chapter 28). Basic principles of production not included elsewhere are:

- the work area must be free from materials, products, residues or documents that are not related to the current operation

- environmental conditions should be suitable and should be monitored. If intermediate or bulk products are to be stored, even for a short time, they should be kept under appropriate conditions
- significant deviations from expected yield should be recorded and investigated. It is up to the manufacturer to define what is significant but this is often apparent by examining trends after several batches have been made.

An area not well covered by GMP guidelines is the requirement for a procedure to control and investigate any deviations from the standard procedure (Chapter 27). This is an important topic for the manufacturer to cover because deviations often require urgent evaluation and decision-making, unlike controlled changes, which more often than not can be evaluated in a less frenetic atmosphere. The starting point for a deviation procedure must of course be the assumption that operator training clearly instructs that no deviation from the laid-down process can be allowed. However, mistakes do occur. In addition equipment breaks down, power cuts happen which are outside anyone's control. All of these potential events need some thought on how they will be evaluated. A sound deviations procedure is most important in this respect.

26.2.5.6 Packaging Materials. Because packaging problems are the most frequent cause of product recalls worldwide, it is not surprising that no less attention must be given to their source and control than to raw materials. Similar attention to selection and monitoring of suppliers is required. It should be remembered that suppliers of printed packaging and manufacturers of packaging items such as bottles, closures and blister foils more often than not supply many other non-medicine industries. The consequences of label mix-ups, or poor closure/bottle fitting may not be so "exciting" to those outside the pharmaceutical industry.

26.2.5.7 Packaging Operations. It is at the packaging stage that the opportunity for major errors really presents itself. All those involved within packaging operations should be vigilant to the possibilities of mix-ups of product, labels and leaflets and other printed matter. Packaging areas are usually very busy with several lines operating side by side, albeit suitably separated. Packaging operators and in particular engineering fitters move from line to line as production requirements dictate. These movements carry the potential for small items such as tablets, capsules, ampoules and vials to be carried accidentally from one line to another. Most packaging lines nowadays use self-adhesive labels supplied on rolls, which minimise the likelihood of an odd label drifting about. Nevertheless, those who still use individually cut labels must be especially vigilant.

Thus procedures in the packaging area should control product and materials coming to the area from the stores. Operators must be trained to recognise subtle differences between similar products and packaging. Line clean-down and start-up procedures must ensure that residues of previous product and packaging are removed and checks made to ensure the line is clear.

During the packaging operations routine checks should be carried out to ensure that the integrity of the pack remains in control. Such checks include confirmation that overprinted information remains correct and legible, that labels, leaflets and cartons are of the correct identity and that closure and seal integrity is within the expected limits.

Example 8: During a long packaging operation more labels were required. Labels for the product with the correct name but different strength were issued by the store. Because they arrived on the line at a shift change over they went unnoticed and part of the batch was distributed with incorrect labels.

An important aspect of packaging is the reconciliation procedure after a batch is completed. Reconciliation must take into account both the product and packaging which was:

- sent to the line
- used in the pack

- lost during packaging
- left over.

Procedures should also be clear on what to do with the leftover product and packaging. Owing to the danger of mix-ups some companies do not return opened cartons of leaflets or printed items to the store. Any product left over may also be uneconomic to keep when the dangers of mix-ups are considered.

26.2.5.8 Finished Products (Chapter 28). Storage procedures should ensure that any finished product cannot be released for distribution until it has been released. At all times it should be stored under suitable conditions. Sometimes it is necessary to pack products at room temperature, which must then be cold stored to maintain shelf life. If that is the case, the maximum time allowed at room temperature should be stated.

26.2.5.9 Rejected, Recovered and Returned Materials. The careful control of rejected materials is paramount, especially if they are products from within the manufacturing site itself. They must be labelled properly and stored in a separated and designated area. Access to this area should be restricted.

Any reprocessing of a rejected product should be exceptional and requires full evaluation to ensure that the final quality of the product will not be affected. Recovery of products from batches which did conform to the required quality, requires prior approval within the marketing authorisation. Recovered material may require additional testing to confirm the quality.

26.2.6 Quality Control

26.2.6.1 General. There is a fundamental requirement for the manufacturer to have a QC department that must be independent of all other departments. The continued use by all regulatory authorities of the term ''QC'' has changed the historic perception of this department, which must have authority for all decisions related to quality. Indeed, the Head of QC should be an authoritative figure, with the qualifications, training and experience necessary for the particular function (The responsibilities of this position were provided under ''Personnel'' above). Quality Control staff must also be allowed access to all production areas to allow sampling and investigation if required.

The QC department is also expected to establish, validate and implement all QC procedures, keep reference samples, ensure correct labelling, ensure stability monitoring and participate in complaints investigations. Most modern pharmaceutical organisations delegate these responsibilities to a department known as ''Quality Assurance'' but the independence from other departments must be maintained.

GMP emphasises that finished-product assessment is not simply a question of testing samples to see if they comply with a specification. All factors which might have an effect on quality must be taken into account, including environmental conditions, review of production and packaging records and examination of the finished pack.

26.2.6.2 Good Quality Control Laboratory Practice (GCLP) (Chapter 30). Good quality control laboratory practice is a subdivision of GMP related to proper organisation and management of the laboratory operations related to testing medicinal products. GCLP should be distinguished from good laboratory practice (GLP), which is a term formally reserved for the regulation of animal testing laboratories (Part 2).

A laboratory must have an appropriate documentation system. Since the activities should be governed by the operation of the quality system it follows that the documentation system should be

designed as part of the overall company system. This is often found not to be the case, leading to confusion of definitions and different levels of quality in documents between the GCLP system and the main GMP system.

Whatever the system, the QC department has a responsibility to store documents related to the quality of each batch produced. The minimum storage periods are set out as 1 year after the expiry date or, within the EU, 5 years after the certification by a QP. Such records should include all original data such as that found in laboratory notebooks.

Special attention should be drawn to the requirements for sampling. It is recognised that any sample, at best, can only give a snapshot of the quality of the whole batch. Thus samples should be taken with care using trained operators following clear procedures. Any ad hoc samples should be treated carefully, unless they have been taken using a preordained plan. Samples must be labelled with, as a minimum, the contents, batch number, date of sampling and some indication of the containers from which the samples have been drawn.

Reference samples of materials and finished product must be retained. In the case of finished product the minimum period is 1 year after the expiry date. Raw materials should be retained for 2 years after release of the last batch of product containing them. There are exemptions for raw materials which would be hazardous to keep or which are volatile. The size of all samples should permit at least one full set of tests to be carried out. In the case of finished products the manufacturer should ensure that the sample is not lost to retesting early on in the shelf life by retaining sufficient for several retests.

Analytical methods should be validated (Chapter 30) and in any case all tests should be carried out in accordance to the marketing authorisation. Subtle changes, which ''improve'' the methods, must be avoided unless properly authorised by the appropriate authorities.

Example 9: An analyst adjusted the wavelength at which an HPLC method was carried out to obtain a sharper peak of the active ingredient. A related substance, not normally found in the product but which was quoted in the active ingredient specification, was missed because it did not absorb well at the new wavelength. This related substance was subsequently found during stability studies and the batch had to be recalled.

The Guide to GMP lists the requirements for the test records[13] and specifies the minimum standards for laboratory reagents and glassware.

26.2.7 Contract Manufacture and Analysis

Many holders of marketing authorisations do not also hold a manufacturing authorisation. Even the holder of a manufacturing authorisation itself might require additional services to those which he can provide within his own organisation. The Guide to GMP provides a structure around which such arrangements should be made. It describes the role of the ''Contract Giver'', that is someone who wants work carried out on his behalf; and the ''Contract Acceptor'' or the person who agrees to carry out that work.

Holders of marketing and manufacturing authorisations have responsibilities to ensure that any product is manufactured and tested according to the terms of the marketing authorisation. When such responsibilities are delegated it is vital that a written contract is drawn up between the parties, which clearly sets out who will discharge those responsibilities and how communication will occur.

Proper lines of communication are especially important with respect to approved changes to the formulation, process or tests. Additionally the responsibility for certification by the QP and product release must be clear.

The Contract Giver must be given access to the Contract Acceptor's premises and any records related to the products. The Contract Acceptor must not engage in any activity detrimental to the contracted products.

It should be noted that contract facilities must be approved and included on the appropriate manufacturing and marketing authorisations. Contract laboratories are subject to regulatory inspection, whether they are part of an organisation which holds a manufacturing authorisation or not.

26.2.8 Complaints and Product Recall

26.2.8.1 Complaints. Manufacturers must have a written procedure for dealing with complaints and a responsible person should be designated to handle all complaints. This ensures that if a series of complaints is received related to the same product or a particular batch it is recognised as requiring serious attention immediately. If applicable, the QP must be made aware of all complaints since he or she might have to take the initiative to recall a batch of product.

The complaints procedure should ensure that a proper and timely investigation is carried out to determine the probable cause of any complaint and to decide if there is a serious defect. The consequences for other batches of the same product or for other products (*e.g.* in the case of a packaging defect or defect raw material) must be taken into account. The complaint procedure should also involve other departments and appropriate disciplines such as medical and regulatory affairs groups within the company, to provide an assessment of criticality.

26.2.8.2 Recalls. As in the case of complaints, there should be a written procedure that lays down the action to be taken in the event that a decision to recall a batch or batches of product has to be taken. A designated person should be responsible for co-ordinating the company's actions and for communicating with regulatory authorities.

Since any recall may require urgent and immediate action the procedure should be capable of operating at any time, including weekends and holidays. It is especially important that those who are in charge of the distribution records can be contacted and are capable of providing them at a moment's notice.

Most regulatory agencies have a specific department that must be notified in the event of a defective product which might be recalled or which is being recalled. The contact address and telephone and fax numbers should be included within the procedure and regularly checked to ensure it remains current.

Any products which are returned due to being recalled must be held in a separated and controlled location within the storage facility. They should be properly labelled as their status and destroyed as soon as possible after the recall is judged to be complete. The person responsible for the recall should issue a written report to include reconciliation, as far as possible.

The recall procedure should be evaluated on a regular basis for its effectiveness. This is often done by carrying out a "dummy" recall by choosing a batch and determining how rapidly information on its distribution can be gathered. The dummy run should also test the availability of key contacts and whether contacts are up-to-date. It is not sufficient to treat a real recall as this dummy test, since all the elements of the procedure might not have been tested.

26.2.9 Self-Inspection

The effectiveness and currency of the Quality System must be regularly evaluated by means of a self-inspection programme. Elements of a successful and effective programme are:

- a procedure for conducting self-inspections naming those who should carry them out. Preferably they should be carried out by an independent individual, accompanied by those responsible for the area under inspection
- a matrix of areas, systems, and facilities to be inspected against a planned schedule

- written reports with recommendations for improvement
- senior-management review of planned and completed corrections.

26.3 CONCLUSION

This chapter has summarised the requirements of GMP, mainly according to the expectations of the European Guide to GMP. The examples provided indicate the major defects that can occur due to apparently minor or simple actions by untrained or unthinking individuals. Detailed requirements for manufacturing controls on specific areas of production or specific types of products are found in the Annexes of the Guide to GMP, which should be consulted if applicable. The requirements for the GMP manufacture of IMP for clinical trials are detailed in Chapter 29.

GMP is an evolving and dynamic requirement. The community expects continuously improved assurance of safety and quality from its medicines. Practices which were acceptable even a few years ago are no longer satisfactory. The manufacturer and especially those responsible for the implementation and maintenance of GMP should constantly be aware of that.

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13. See ref. 8 at 6.17.